original reports

Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study

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abstract

PURPOSE Patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC) have poor prognosis. For these patients, treatment options are limited after first-line systemic therapy.

PATIENTS AND METHODS In this open-label phase III clinical study, patients with advanced or metastatic ESCC, whose tumor progressed after first-line systemic treatment, were randomly assigned (1:1) to receive intravenous tislelizumab, an anti–programmed cell death protein 1 antibody, 200 mg every 3 weeks or chemotherapy (investigator's choice of paclitaxel, docetaxel, or irinotecan). The primary end point was overall survival (OS) in all patients. The key secondary end point was OS in patients with programmed death-ligand 1 tumor area positivity (TAP) score ≥ 10%.

RESULTS In total, 512 patients across 11 countries/regions were randomly assigned. At final analysis, conducted after 410 death events occurred, OS was significantly longer with tislelizumab versus chemotherapy in all patients (median, 8.6 *v* 6.3 months; hazard ratio [HR], 0.70 [95% CI, 0.57 to 0.85]; one-sided $P = .0001$), and in patients with TAP ≥ 10% (median, 10.3 months *v* 6.8 months; HR, 0.54 [95% CI, 0.36 to 0.79]; one-sided $P = .0006$). Survival benefit was consistently observed across all predefined subgroups, including those defined by baseline TAP score, region, and race. Treatment with tislelizumab was associated with higher objective response rate (20.3% *v* 9.8%) and a more durable antitumor response (median, 7.1 months *v* 4.0 months) versus chemotherapy in all patients. Fewer patients experienced ≥ grade 3 treatment-related adverse events (18.8% *v* 55.8%) with tislelizumab versus chemotherapy.

CONCLUSION Tislelizumab significantly improved OS compared with chemotherapy as second-line therapy in patients with advanced or metastatic ESCC, with a tolerable safety profile. Patients with programmed death-ligand 1 TAP ≥ 10% also demonstrated statistically significant survival benefit with tislelizumab versus chemotherapy.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In 2020, esophageal cancer (EC) was ranked the seventh most common cancer worldwide and sixth most common cause of cancer-related deaths.[1] Esophageal squamous cell carcinoma (ESCC) is the most common histologic subtype, accounting for more than 85% of ECs worldwide.[2,3] Reports from the SEER Program show that between 2011 and 2017, the prognosis of metastatic ESCC was poor, with a 5-year survival rate of 5.2%.[4]

First-line systemic therapy for advanced or metastatic ESCC typically consists of a fluoropyrimidine- and platinum-based regimen.[5-7] In the second-line setting, single-agent taxane or irinotecan is typically used; however, these are associated with significant toxicities and marginal antitumor activity with poor long-term survival.[8-12] Recently, trials studying the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway have demonstrated prolonged survival and safety benefits with anti–PD-1 antibodies versus

CONTEXT

Key Objective

Esophageal squamous cell carcinoma (ESCC) is an aggressive cancer associated with a 5-year survival rate of 5%. The phase III RATIONALE-302 study that enrolled a global population of 512 patients with advanced or metastatic ESCC evaluated whether tislelizumab monotherapy improved overall survival versus chemotherapy when used as second-line treatment for patients with advanced or metastatic ESCC.

Knowledge Generated

Tislelizumab demonstrated statistically significant and clinically meaningful improvement in overall survival versus chemotherapy, with a tolerable safety profile, in patients with advanced or metastatic ESCC in a global population in second-line treatment. In patients with programmed death-ligand 1 tumor area positivity ≥ 10%, tislelizumab also demonstrated statistically significant survival benefit. Survival benefit of tislelizumab over chemotherapy was observed across subgroups of region, race, and programmed death-ligand 1 expression level.

Relevance

The results of RATIONALE-302 suggest that tislelizumab is an appropriate treatment option for patients with advanced or metastatic ESCC in second-line treatment setting.

chemotherapy in patients with advanced or metastatic ESCC whose disease progressed after first-line systemic therapy.[10-13] These studies demonstrated survival benefit specifically in patients with high PD-L1 expression, or in Asian or Chinese patients irrespective of PD-L1 expression level.[10-12]

Tislelizumab is an investigational humanized immunoglobulin G4 monoclonal antibody with high affinity for PD-1, designed to minimize binding to FcγR on macrophages to limit antibody-dependent phagocytosis, a potential mechanism of resistance to anti–PD-1 therapy.[14] In early-phase clinical studies, tislelizumab monotherapy or in combination with chemotherapy demonstrated antitumor activity in patients with solid tumors, including ECs, and showed a safety profile similar to other anti–PD-1 antibodies.[15-17] Here, we report the efficacy and safety results from the global, randomized phase III RATIONALE-302 study (ClinicalTrials.gov identifier: NCT03430843) of tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic ESCC.

PATIENTS AND METHODS

Patients

Eligible patients were adults (age ≥ 18 years) with histologically confirmed ESCC who had advanced or metastatic disease that progressed after first-line systemic treatment. Patients who had tumor progression within 6 months after definitive chemoradiotherapy, neoadjuvant, or adjuvant therapy were also eligible. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, at least one measurable/evaluable lesion by RECIST v1.1, and adequate hematologic, hepatic, renal, and coagulation function. Exclusion criteria included patients who had received prior therapies targeting PD-1 or PD-L1, active brain or leptomeningeal metastasis, active autoimmune disease, or other prior malignancies active within 2 years before random assignment. Full eligibility criteria are provided in the Data Supplement (online only).

The Protocol (online only) was approved by the relevant Institutional Review Board/Independent Ethics Committee for each study site. The full Protocol is available with the Data Supplement. The study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and local laws and regulations. All patients provided written informed consent before participation.

Trial Design and Treatment

This open-label, randomized, active-controlled, multicenter, phase III clinical study recruited patients across 11 countries/regions (Belgium, mainland China, France, Germany, Italy, Japan, Republic of Korea, Spain, Taiwan, the United Kingdom, and the United States). Eligible patients were randomly assigned (1:1) to receive tislelizumab or investigator's choice of the following single-agent chemotherapies: paclitaxel, docetaxel, or irinotecan. Tislelizumab was administered intravenously (IV) 200 mg once every three weeks. Paclitaxel was administered as 135-175 mg/m^2 IV once every 3 weeks, or in doses of 80-100 mg/m^2 once weekly as per regional guidelines. In Japan, paclitaxel was administered as 100 mg/m^2 IV in cycles consisting of once weekly dosing for 6 weeks, followed by one week of rest. Docetaxel was administered as 75 mg/m^2 IV once every 3 weeks (70 mg/m^2 IV once every 3 weeks in Japan). Irinotecan 125 mg/m^2 IV was administered on days 1 and 8, every 21 days. Stratified randomization was used and was stratified by region (Asia [excluding Japan] *v* Japan *v* Europe/North America), ECOG PS (0 *v* 1), and investigator-chosen chemotherapy (paclitaxel *v*

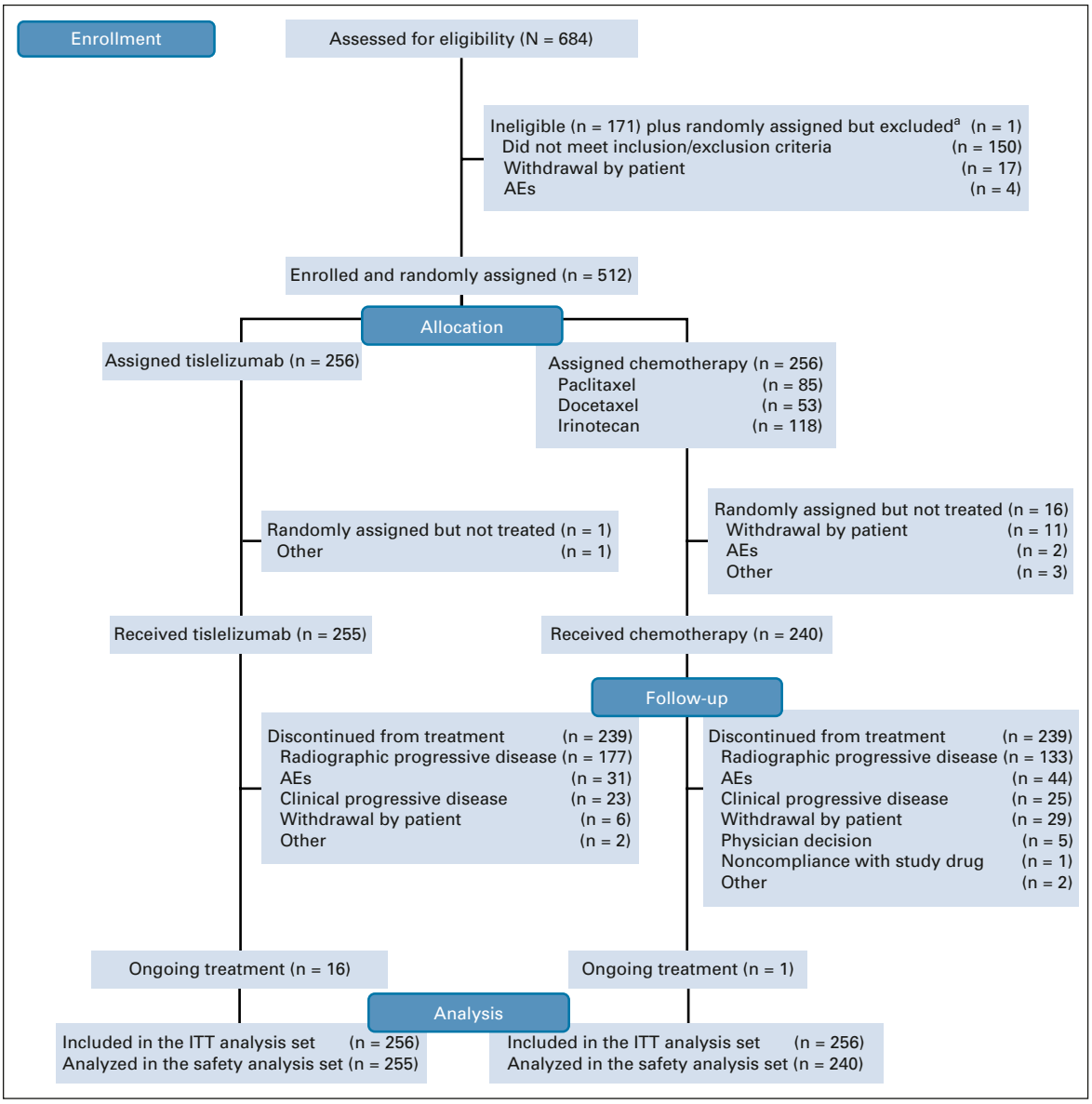

FIG 1. CONSORT diagram. [a]One patient died before random assignment and was inadvertently randomly assigned into the study. Data cutoff: December 1, 2020. AE, adverse event; ITT, intent-to-treat.

docetaxel *v* irinotecan). Patients were treated until disease progression, unacceptable toxicity, or withdrawal for other reasons. At the discretion of the investigator, patients receiving tislelizumab could continue to receive treatment after progression if the patient was likely to benefit from continued treatment, provided that the patient provided written informed consent. Details of random assignment and tumor response assessment methods are described in the Data Supplement.

Assessments

PD-L1 expression was centrally assessed using the analytically validated VENTANA PD-L1 (SP263) assay with tumor area positivity (TAP) score, which is defined as the total percentage of the tumor area covered by tumor cells with any membrane staining above background and tumor-associated immune cells with any staining above background. Patients with PD-L1–positive expression were defined as having a TAP score of ≥ 10%. Tumor responses were assessed using computed tomography or magnetic resonance imaging, every 6 weeks for 6 months, and then every 9 weeks, by the investigator per RECIST v1.1. Adverse events (AEs) were assessed throughout the study and up to 30 days after the last dose of study drug or initiation of a new anticancer therapy, whichever occurred first, according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Immune-related AEs were recorded up to 90 days after the last dose of study drug,

TABLE 1. Patient Demographics and Baseline Characteristics in the Intent-to-Treat Population

Characteristic	Tislelizumab (n = 256)	Chemotherapy (n = 256)
Age, years, median (range)	62.0 (40-86)	63.0 (35-81)
< 65, No. (%)	157 (61.3)	161 (62.9)
≥ 65, No. (%)	99 (38.7)	95 (37.1)
Sex, No. (%)		
Male	217 (84.8)	215 (84.0)
Female	39 (15.2)	41 (16.0)
Race, No. (%)		
Asian	201 (78.5)	207 (80.9)
White or Caucasian	53 (20.7)	44 (17.2)
Black or African American	0 (0.0)	2 (0.8)
Other	0 (0.0)	1 (0.4)
Not reported/unknown	2 (0.8)	2 (0.8)
Geographic region, No. (%)		
Asia[a]	201 (78.5)	203 (79.3)
Europe/North America	55 (21.5)	53 (20.7)
ECOG PS, No. (%)		
0	66 (25.8)	60 (23.4)
1	190 (74.2)	196 (76.6)
PD-L1 expression, No. (%)		
TAP ≥ 10%	89 (34.8)	68 (26.6)
TAP < 10%	116 (45.3)	140 (54.7)
Unknown	51 (19.9)	48 (18.8)
Smoking status, No. (%)		
Never	68 (26.6)	63 (24.6)
Former/current	188 (73.4)	192 (75.0)
Missing	0 (0.0)	1 (0.4)
Previous therapies, No. (%)		
Surgery	94 (36.7)	99 (38.7)
Radiotherapy	169 (66.0)	163 (63.7)
Platinum-based chemotherapy	249 (97.3)	252 (98.4)
Disease stage at study entry, No. (%)		
Locally advanced	5 (2.0)	20 (7.8)
Metastatic	251 (98.0)	236 (92.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

[a]There were 50 patients from Japan: 25 patients in the tislelizumab arm and 25 patients in the chemotherapy arm.

regardless of whether the patient started a new anticancer therapy. All suspected study-drug–related serious AEs continued to be recorded by the investigators after treatment discontinuation.

End Points

The primary end point of this study was overall survival (OS) in all randomly assigned patients (the intent-to-treat [ITT] population). The key secondary end point was OS in patients with PD-L1 TAP ≥ 10%. Other secondary end points included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR), assessed by the investigator per RECIST v1.1 in the ITT population and in patients with PD-L1 TAP ≥ 10%, and safety and tolerability. A complete list of study end points is provided in the Data Supplement.

Statistical Analyses

The OS hazard ratio (HR) of interest for tislelizumab versus chemotherapy was assumed to be 0.75 with a median OS of 8 versus 6 months, respectively. Approximately 400 death events were required to provide a power of 82% at a one-sided significance level of 0.025 to detect superiority of tislelizumab over chemotherapy. Assuming a 26-month period to observe the target number of death events and a dropout rate of 5% per year, approximately 500 patients were to be enrolled. The target number of death events was estimated to occur approximately 30.2 months after the first patient enrolled.

For OS analysis, *P* values for the comparison between treatment arms were estimated from a one-sided log-rank test stratified by ECOG PS and investigator-chosen chemotherapy. HRs and associated two-sided 95% CIs were estimated from a stratified Cox regression model including treatment arm as a covariate and with chemotherapy option and ECOG PS as strata. Median OS and 95% CI were calculated using a generalized Brookmeyer and Crowley method, and the cumulative probability of OS at 6 and 12 months was calculated (with two-sided 95% CI) using Greenwood's formula. Kaplan-Meier survival curves were also presented for each arm. When superiority in OS in the ITT population was determined, a hierarchical hypothesis testing approach for the key secondary end point of OS in patients with PD-L1 TAP ≥ 10% was used to preserve a study-wise type I error rate at 5%. The subgroup analysis of OS in the ITT population was prespecified in the Statistical Analysis Plan provided in the Data Supplement.

Median PFS and median DoR with 95% CI were calculated using a generalized Brookmeyer and Crowley method. For ORR, a stratified Cochran-Mantel-Haenszel test was used to calculate common odds ratios and associated two-sided 95% CIs. ORR, difference in ORR, and Clopper-Pearson 95% CI were also calculated.

Safety was evaluated in all randomly assigned patients who received at least one dose of study drug and analyzed using descriptive statistics. All calculations and analyses were conducted using SAS version 9.4 or higher. Full statistical methods are provided in the Statistical Analysis Plan provided in the Data Supplement.

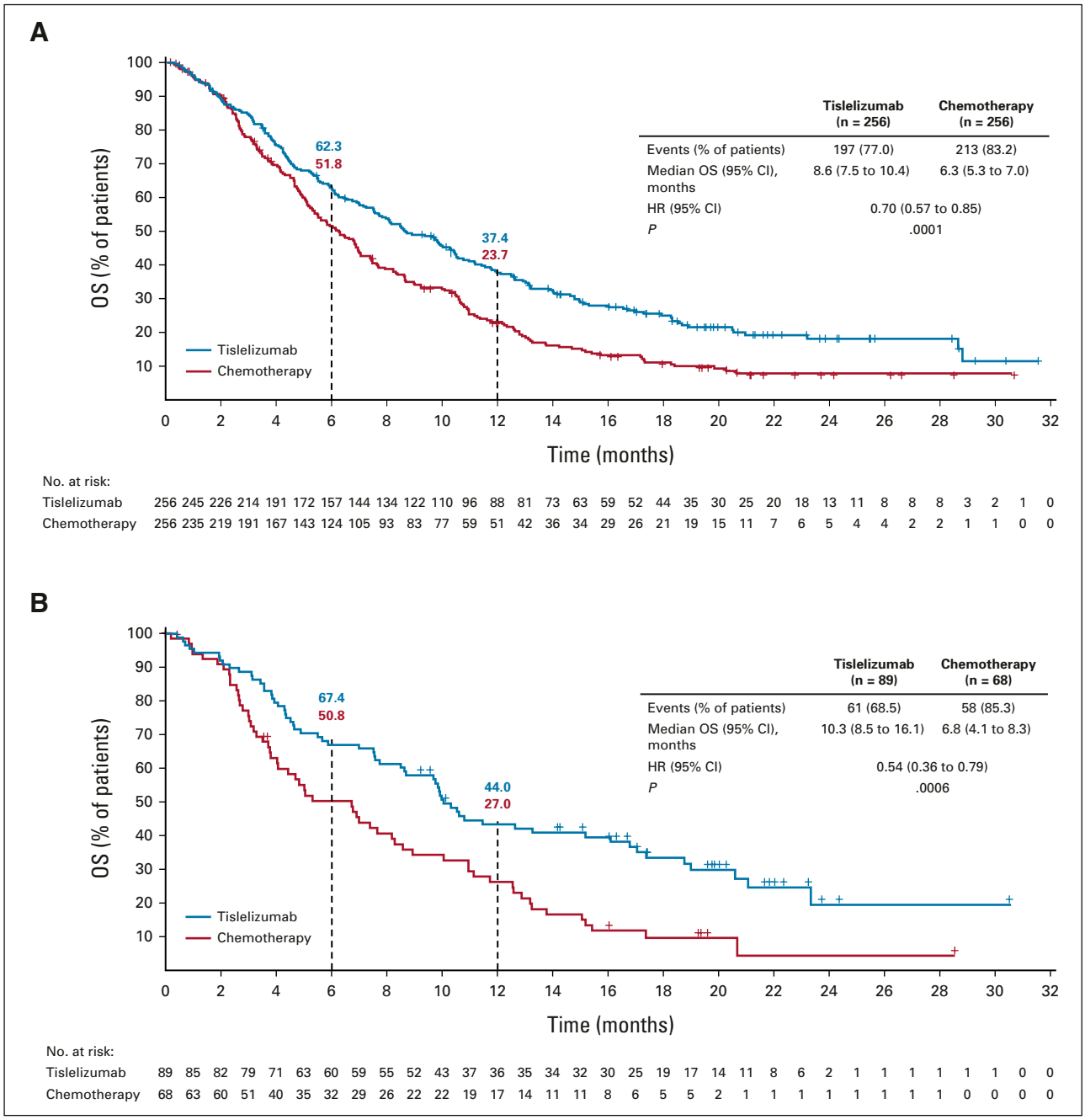

FIG 2. Kaplan-Meier plot of OS in the (A) intent-to-treat population, (B) PD-L1 TAP ≥ 10%, (C) PD-L1 TAP < 10%, and (D) TAP unknown populations. One-sided *P* value was estimated from a log-rank test stratified by ECOG PS and chemotherapy option. HR was based on a Cox regression model including treatment as a covariate and ECOG PS and chemotherapy option as strata. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumor area positivity. (continued on following page)

RESULTS

Patients and Treatment

Between January 2018 and March 2020, 512 patients in Asia (404 patients [78.9%]) and Europe and North America (108 patients [21.1%]) were randomly assigned to receive tislelizumab (n = 256) or chemotherapy (n = 256) and were included in the ITT population (Fig 1). Of these, 255 patients in the tislelizumab arm and 240 patients in the chemotherapy arm received at least one dose of assigned treatment (Fig 1). Patient characteristics and demographics were generally balanced between treatment arms (Table 1). The median age of patients was 62 years, 79.7% of patients were Asian, and 84.4% of patients were male. A total of 487 (95.1%) patients had metastatic disease at study entry, and 157 (30.7%) patients had PD-L1 TAP ≥ 10% tumors. More patients in the

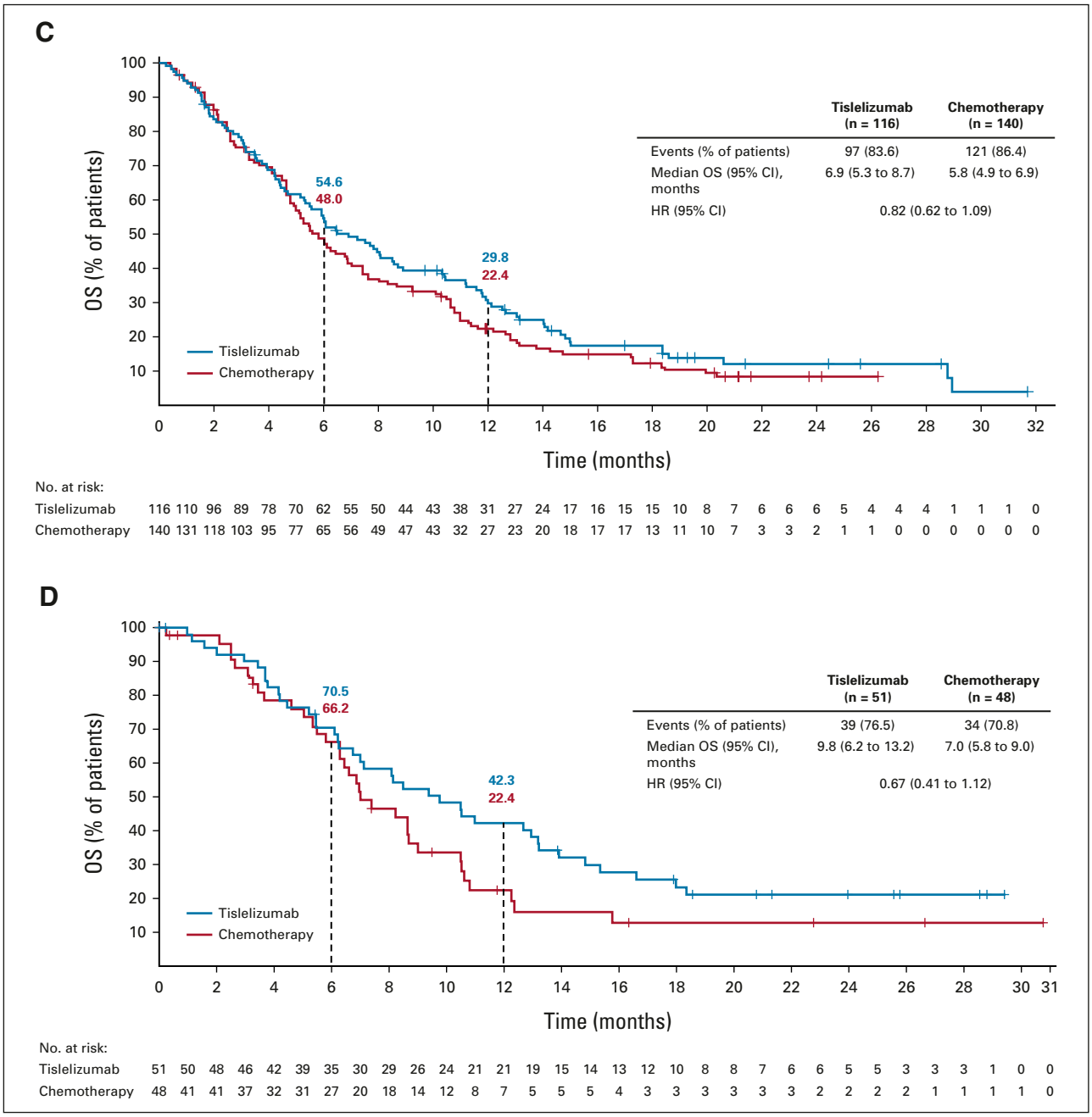

FIG 2. (Continued).

tislelizumab arm had PD-L1 TAP ≥ 10% versus patients in the chemotherapy arm (34.8% *v* 26.6%).

At the time of data cutoff (December 1, 2020), median follow-up from random assignment to data cutoff or death, whichever came first, was 8.5 months (0.2 to 31.7 months) for tislelizumab and 5.8 months (0.0 to 30.8 months) for chemotherapy. The median duration of exposure was 84.0 days (7-862 days) to tislelizumab and 45.5 days (7-584 days) to chemotherapy. More patients in the tislelizumab arm received ≥ 6 months of study treatment versus patients in the chemotherapy arm (25.5% *v* 8.7%).

Efficacy

At final analysis, a total of 197 (77.0%) versus 213 (83.2%) deaths occurred in the tislelizumab and chemotherapy arms, respectively. OS was significantly improved in the tislelizumab arm versus the chemotherapy arm (median 8.6 months [95% CI, 7.5 to 10.4] *v* 6.3 months [95% CI, 5.3 to 7.0]; HR for death 0.70, 95% CI, 0.57 to 0.85; one-sided $P = .0001$; Fig 2). The 12-month OS rate was 37.4% (95% CI, 31.4 to 43.4) versus 23.7% (95% CI, 18.5 to 29.3) in the tislelizumab and chemotherapy arms, respectively. In total, 11 patients

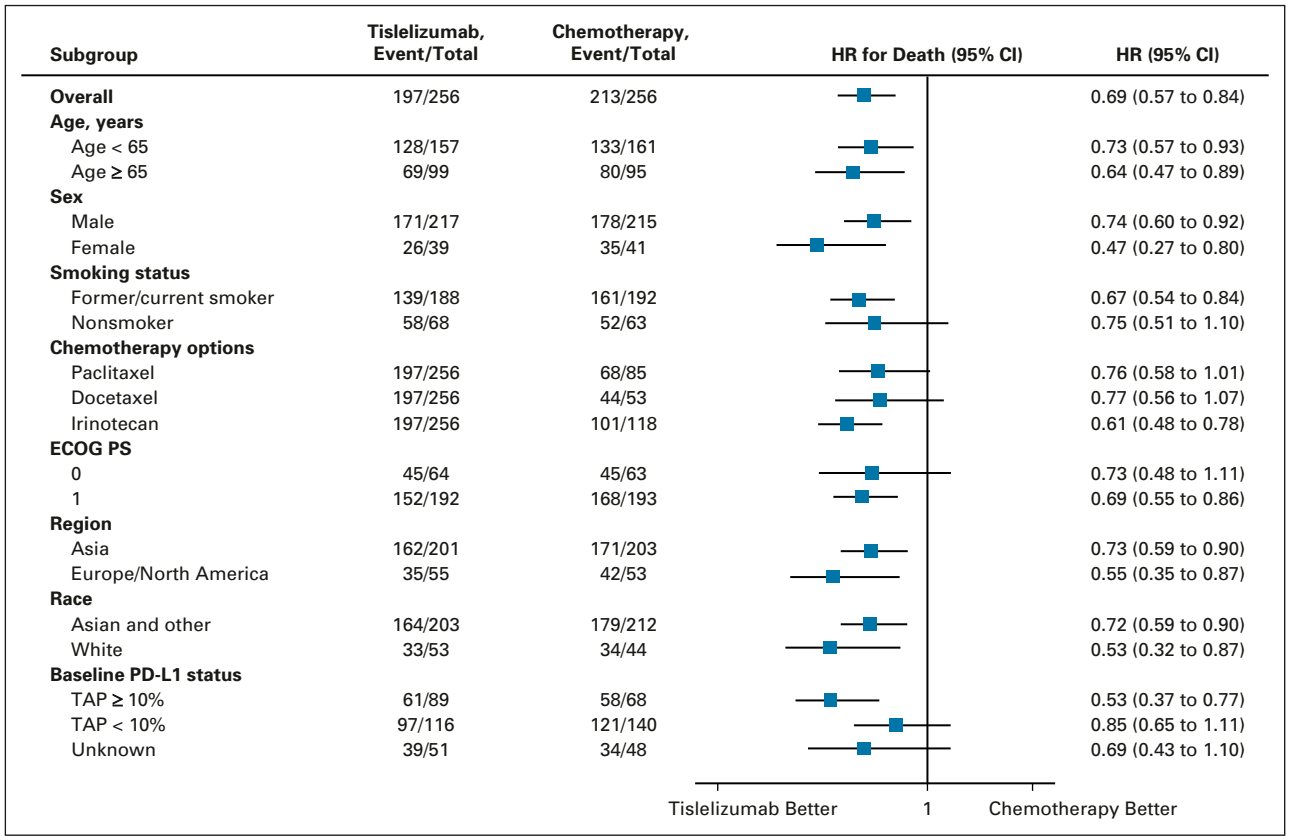

FIG 3. Subgroup analysis of overall survival in the intent-to-treat population. HR was based on an unstratified Cox regression model including treatment as a covariate. The race subcategory other includes Black or African American, not reported, unknown, and other. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

(4.3%) versus 55 patients (21.5%) in the tislelizumab and chemotherapy arms, respectively, had received anti–PD-1 or anti–PD-L1 therapy after discontinuation of study treatment (Data Supplement). Post hoc adjustment analyses for baseline PD-L1 expression status confirmed that the imbalance between treatment arms in baseline PD-L1 expression status had little impact on the estimate of the treatment effect on OS results (Data Supplement). Survival benefit of tislelizumab versus chemotherapy was observed in all predefined subgroups, including those defined by baseline PD-L1 expression status, region, and race (Fig 3; Data Supplement).

In patients with TAP ≥ 10%, tislelizumab significantly improved OS versus chemotherapy (median 10.3 months; 95% CI, 8.5 to 16.1 *v* 6.8 months; 95% CI, 4.1 to 8.3; HR 0.54; 95% CI, 0.36 to 0.79; one-sided $P = .0006$; Fig 2, Data Supplement). Survival benefits with tislelizumab versus chemotherapy were also observed in patients with TAP < 10% (HR, 0.82; 95% CI, 0.62 to 1.09) and TAP unknown (HR, 0.67; 95% CI, 0.41 to 1.12; Fig 2, Data Supplement). The post hoc interaction analysis between treatment group and baseline PD-L1 expression status showed the *P* value was .21, indicating no significant interaction of treatment effect by PD-L1 status (*P* value ≥ .15).

A total of 223 (87.1%) versus 180 (70.3%) patients had disease progression or died at data cutoff in the tislelizumab and chemotherapy arms, respectively. Median PFS was 1.6 months (95% CI, 1.4 to 2.7) versus 2.1 months (95% CI, 1.5 to 2.7) in the tislelizumab and chemotherapy arms, respectively (HR, 0.83; 95% CI, 0.67 to 1.01; Fig 4). The PFS Kaplan-Meier curves began to separate at approximately 3 months in favor of tislelizumab versus chemotherapy. The estimated PFS rates in the tislelizumab versus chemotherapy arms were 21.7% versus 14.9% at 6 months and 12.7% versus 1.9% at 12 months (Fig 4). PFS results in patients with TAP ≥ 10% are shown in the Data Supplement.

A total of 52 patients (20.3% [95% CI, 15.6 to 25.8]) in the tislelizumab arm versus 25 patients (9.8% [95% CI, 6.4 to 14.1]) in the chemotherapy arm achieved an objective response (Table 2). Moreover, 5 (2.0%) patients versus 1 (0.4%) patient had a complete response in the tislelizumab and chemotherapy arms, respectively. Median DoR was 7.1 months (95% CI, 4.1 to 11.3) in the tislelizumab arm versus 4.0 months (95% CI, 2.1 to 8.2) in the chemotherapy arm (Table 2, Fig 4). ORR also favored tislelizumab versus chemotherapy in patients with TAP ≥ 10% (Data Supplement).

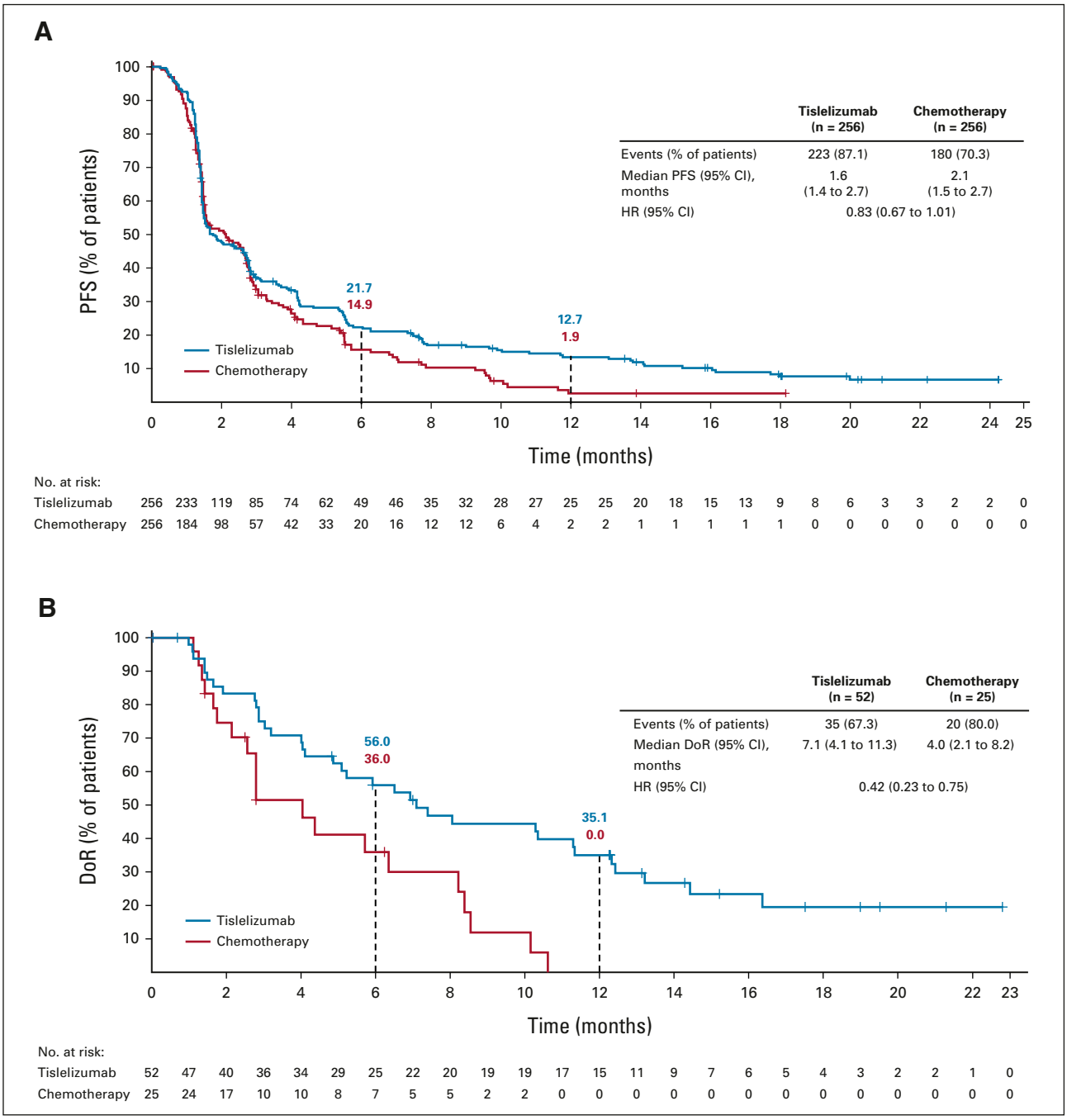

FIG 4. Kaplan-Meier plot of (A) PFS and (B) DoR in the intent-to-treat population. HR was based on a Cox regression model including treatment as a covariate and Eastern Cooperative Oncology Group performance status and chemotherapy option as strata. DoR, duration of response; HR, hazard ratio; PFS, progression-free survival.

Safety and Tolerability

Fewer patients experienced treatment-related AEs (TRAEs) with tislelizumab versus chemotherapy (73.3% *v* 93.8%; Table 3). The most common TRAEs with tislelizumab were increased aspartate aminotransferase (11.4%), anemia (11.0%), and hypothyroidism (10.2%). The most common TRAEs with chemotherapy were decreased white blood cell count (40.8%), decreased neutrophil count (39.2%), and anemia (34.6%). Fewer patients had ≥ grade 3 TRAEs with tislelizumab versus chemotherapy (18.8% *v* 55.8%). The incidence of serious TRAEs was 14.1% versus 19.6% with tislelizumab versus chemotherapy, respectively. Fewer patients discontinued tislelizumab versus chemotherapy (6.7% *v* 13.8%) because of a TRAE (Table 3).

In both treatment arms, the primary cause of death was disease progression, which occurred at a lower frequency

TABLE 2. Summary of Antitumor Activity

Antitumor Response	Tislelizumab (n = 256)	Chemotherapy (n = 256)
ORR, No. (%) [95% CI][a]	52 (20.3) [15.6 to 25.8]	25 (9.8) [6.4 to 14.1]
Odds ratio for ORR (95% CI)	2.39 (1.42 to 4.01)	
Best overall response, No. (%)		
Complete response	5 (2.0)	1 (0.4)
Partial response	47 (18.4)	24 (9.4)
Stable disease	68 (26.6)	82 (32.0)
Progressive disease	116 (45.3)	86 (33.6)
Not evaluable[b]	1 (0.4)	3 (1.2)
Not assessable[c]	19 (7.4)	60 (23.4)
DoR, months, median (95% CI)[a]	7.1 (4.1 to 11.3)	4.0 (2.1 to 8.2)
Patients with ongoing response, No./n (%)	10/52 (19.2)	0/25 (0.0)

Abbreviations: DoR, duration of response; ORR, overall response rate.

[a]ORR and DoR results were based on unconfirmed tumor responses.

[b]Not evaluable on the basis of RECIST v1.1.

[c]Patients with no postbaseline tumor assessment by data cutoff, including those who discontinued study for any reason or died without having any postbaseline tumor assessment.

with tislelizumab versus chemotherapy (59.8% *v* 66.0%). Deaths attributed to TRAEs were reported for 5 (2.0%) patients in the tislelizumab arm versus 7 (2.9%) patients in the chemotherapy arm.

DISCUSSION

The RATIONALE-302 phase III study was designed to detect the superiority of tislelizumab versus chemotherapy in improving survival in all randomly assigned patients and met this primary end point at final analysis. Treatment with tislelizumab showed a statistically significant and clinically meaningful improvement in OS versus chemotherapy in patients with advanced or metastatic ESCC whose disease progressed during or after first-line therapy. Survival benefit was observed across all prespecified subgroups, including region, race, and PD-L1 expression level.

RATIONALE-302 was, to our knowledge, the first study that demonstrated significant survival benefit with an anti–PD-1 antibody in a global ESCC population from Asia and Europe/North America. The OS improvement (30% reduction in the risk of death and 2.3-month extension in median OS) was similar to other studies investigating anti–PD-1 antibodies as second-line treatment for ESCC.[10,12] In ATTRACTION-3, which mainly enrolled Asian patients (96%), OS was significantly improved with nivolumab versus chemotherapy (paclitaxel or docetaxel): 10.9 months versus 8.4 months, HR = 0.77, $P = .019$.[10] In ESCORT, a study conducted in solely in China, significant improvement in OS was seen with camrelizumab versus chemotherapy (docetaxel or irinotecan): 8.3 months versus 6.2 months, HR = 0.71, $P = .001$.[12] KEYNOTE-181 was a global study that enrolled patients with ESCC and esophageal adenocarcinoma. However, its favorable improvement in OS with pembrolizumab versus chemotherapy (paclitaxel, docetaxel, or irinotecan) in patients with ESCC (8.2 months *v* 7.1 months, HR = 0.78, $P = .0095$) failed to meet the prespecified boundary for statistical significance.[11] Notably, the magnitude of OS benefit with tislelizumab in the RATIONALE-302 study was observed in the context of a much higher rate of subsequent anti–PD-1/PD-L1 treatment after discontinuing from study treatment in the chemotherapy arm (21.5%) versus the tislelizumab arm (4.3%), whereas in other studies, 6%-9% of patients in the chemotherapy arm received subsequent anti–PD-1/PD-L1 antibodies.[10,12]

RATIONALE-302 enrolled 79% of patients from Asia and 21% of patients from Europe/North America, which reflected the global distribution of patients with ESCC. The survival benefit of tislelizumab versus chemotherapy was observed in both Asian (HR, 0.73) and non-Asian patients (HR, 0.55). Although Asian patients with ESCC in KEYNOTE-181 (58% from Asia) appeared to have enhanced benefit with pembrolizumab versus chemotherapy, this was not observed with other anti–PD-1 antibodies, including tislelizumab in RATIONALE-302 and nivolumab in two other large global phase III studies investigating nivolumab versus placebo in the adjuvant treatment of EC (Checkmate-577) and nivolumab plus chemotherapy versus chemotherapy in first-line treatment of EC (Checkmate-648).[18,19]

RATIONALE-302 enrolled patients regardless of PD-L1 expression status. The TAP score (SP263) used to assess PD-L1 expression demonstrated comparable efficacy association in gastric cancer to CPS (22C3).[20] According to the hierarchical testing, OS was significantly improved with tislelizumab over chemotherapy in patients with PD-L1 TAP ≥ 10% (HR, 0.54), and in the prespecified exploratory analysis, tislelizumab also showed a favorable trend of

TABLE 3. Summary of Adverse Events

Adverse Event	Tislelizumab (n = 255)	Chemotherapy (n = 240)
Patients with at least one TEAE, No. (%)	244 (95.7)	236 (98.3)
≥ Grade 3 TEAE	118 (46.3)	163 (67.9)
Serious TEAE	105 (41.2)	105 (43.8)
TEAE leading to treatment discontinuation	49 (19.2)	64 (26.7)
TEAE leading to death[a]	35 (13.7)	28 (11.7)
Patients with at least one TRAE, No. (%)	187 (73.3)	225 (93.8)
≥ Grade 3 TRAE	48 (18.8)	134 (55.8)
Serious TRAE	36 (14.1)	47 (19.6)
TRAE leading to treatment discontinuation	17 (6.7)	33 (13.8)
TRAE leading to death[a]	7 (2.7)	8 (3.3)
TRAEs occurring in ≥ 10% of patients, No. (%)[b]		
AST increased	29 (11.4)	9 (3.8)
Anemia	28 (11.0)	83 (34.6)
Hypothyroidism	26 (10.2)	0 (0.0)
Fatigue	19 (7.5)	33 (13.8)
Decreased appetite	16 (6.3)	75 (31.3)
Diarrhea	14 (5.5)	66 (27.5)
Asthenia	12 (4.7)	28 (11.7)
Malaise	10 (3.9)	35 (14.6)
Weight decreased	8 (3.1)	25 (10.4)
Nausea	7 (2.7)	66 (27.5)
Leukopenia	7 (2.7)	30 (12.5)
WBC count decreased	5 (2.0)	98 (40.8)
Vomiting	4 (1.6)	43 (17.9)
Constipation	4 (1.6)	25 (10.4)
Neutrophil count decreased	3 (1.2)	94 (39.2)
Neutropenia	2 (0.8)	31 (12.9)
Alopecia	0 (0.0)	42 (17.5)

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a]Death events because of disease progression were excluded. Deaths attributed to TRAEs included one each of hemoptysis, pulmonary arterial hypertension, upper gastrointestinal hemorrhage, pneumonia, and decreased platelet count in the tislelizumab arm, and three of septic shock, and one each of pneumonia, febrile neutropenia, death, and multiple organ dysfunction syndrome in the chemotherapy arm.

[b]By system organ class and preferred term.

improvement in OS versus chemotherapy in patients with PD-L1 TAP < 10% (HR, 0.82). Although the OS benefit appeared to be enriched in patients with PD-L1 TAP ≥ 10% in RATIONALE-302, post hoc analysis of OS with the adjustment for PD-L1 expression status confirmed the OS benefit in all randomly assigned patients (HR, 0.70; 95% CI, 0.57 to 0.87), and post hoc interaction analysis between treatment and baseline PD-L1 expression status showed that OS benefit was observed regardless of PD-L1 expression level. Similarly, consistent survival benefit was also observed across patients with different PD-L1 expression levels with nivolumab and camrelizumab over chemotherapy in ATTRACTION-3 and ESCORT studies, which measured PD-L1 expression status using alternative assays.[10,12]

Consistent with OS findings, tislelizumab showed a greater and more durable antitumor response than chemotherapy. ORR was twice as high with tislelizumab versus chemotherapy. Median DoR was 3.1 months longer with tislelizumab versus chemotherapy, with more responders exhibiting ongoing responses at data cutoff. Although median PFS was shorter with tislelizumab versus chemotherapy, the numerically favorable HR of PFS and increasing separation of the Kaplan-Meier curves after 3 months suggested a potential benefit in PFS. Similar separation of Kaplan-Meier curves of PFS in favor of anti–PD-1 antibodies was also observed in other studies conducted in this setting.[11,12] One hypothesis postulated for this observation is the longer time to the onset of

antitumor effect seen with immunotherapies versus cytotoxic drugs.[21]

Despite longer drug exposure with tislelizumab, fewer TRAEs were observed versus chemotherapy. The incidence of ≥ grade 3 TRAEs, serious TRAEs, and TRAEs leading to treatment discontinuation was also lower in the tislelizumab arm versus the chemotherapy arm. Overall, the safety profile of tislelizumab was favorable over chemotherapy.

Limitations of this study include the open-label study design, which may have affected compliance, and a lack of blinded review of response data by an independent committee, which may have affected response data (ORR, PFS, and DoR). In addition, future studies are needed to explore the analytical concordance of the assays and the predictiveness of PD-L1 TAP expression in ESCC.

In conclusion, tislelizumab provided a statistically significant and clinically meaningful improvement in OS versus chemotherapy in patients with advanced or metastatic ESCC who had disease progression after first-line systemic therapy, with a tolerable safety profile. Patients with PD-L1 TAP ≥ 10% also demonstrated statistically significant survival benefit with tislelizumab versus chemotherapy.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

On request, and subject to certain criteria, conditions, and exceptions, BeiGene, Ltd, will provide access to individual deidentified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to DataDisclosure@beigene.com.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of RATIONALE-302 Investigators

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China	Zhendong Chen
China	Tienna Yi
China	Zuoxing Niu
Korea	Sung-Bae Kim (SC member)
Belgium	Eric Van Cutsem (SC member)
Japan	Hiroki Hara
China	Guohua Yu
China	Jianhua Chen
China	Sheng Hu
Taiwan	Chih-Hung Hsu
Taiwan	Chen-Yuan Lin
France	Jean-Philippe Metges
China	Qing Bi
China	Wang Feng
China	Jun Wu
France	Christophe Borg
Japan	Ken Kato (SC member)
China	Wei Ren
China	Lu Ping
China	Jianhua Shi
China	Honglin Hu
China	Xiaoyan Lin
Taiwan	Yee Chao
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Japan	Taroh Satoh
Japan	Takashi Kojima
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Belgium	Marc Van den Eynde
France	Michel Ducreux
Spain	Mariona Calvo
Spain	Federico Longo
Spain	Antonio Cubillo
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United Kingdom	Hendrik-Tobias Arkenau
United Kingdom	David Cunnningham
United Kingdom	Mark Harrison
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Japan	Yu Sunakawa
Japan	Morihito Okada
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China	Shubin Wang
China	Shirong Cai
China	Yi Jiang
China	Xueyi Zhou
China	Aimin Zang
China	Wang Junping
China	Lei Yang
Belgium	Marc Peeters
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Italy	Libero Ciuffreda
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(continued on following page)

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TABLE A1. List of RATIONALE-302 Investigators (continued)

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